REMARKS/ARGUMENTS

Reconsideration of this application and entry of the foregoing amendments are respectfully requested.

Claim 42 has been amended to make clear that the "predetermined metabolic signal" is a "predetermined extracellular metabolic signal". Basis for the revision can be found, for example, in the statement in the fourth paragraph on page 1 of the present specification to the effect that the metabolic activity of a cell causes changes in the extracellular environment. The present invention is a detection method based on those extracellular changes. Attention is also directed to the penultimate paragraph on page 4 and the definition of "metabolic signals" in the context of a change in the environment surrounding the cell, and to the final sentence in the penultimate paragraph on page 5 and the reference to the cytolytic agents being responsive to a chemical or biochemical **released** from the cell. Further, Fig 1 shows the lipid vesicle particles being assembled extracellularly around the cell 3 (note claim 49). Additional support can be found, for example, in the final paragraph on page 17 and the reference to measurement of carbon dioxide and/or pH change (as metabolic signals) in the **vicinity** (emphasis added) of the microbe.

New claim 69 has been added. Basis for the new claim can be found in the numerous references to bacteria throughout the specification, for example, at page 14, line 21, page 21, line 16, page 31, line 6 and elsewhere.

Claims 42, 45-49, 51 and 64 stand rejected under 35 USC 102(e) as allegedly being anticipated by Smith et al in light of Subbarao et al. Withdrawal of the rejection is submitted to be in order for the reason that follow.

Smith et al relates to a peptide – macromolecule complex for delivering a macromolecule (e.g., a nucleic acid) into a cell. The reference relates primarily to a "delivery technique" and not

an analytical method as claimed here. However, these differences aside, the Smith et al complex is one around which a cell (to which the macromolecule is to be delivered) forms an endosome. In this regard, the Examiner's comments in the first paragraph on page 3 of the Office Action are noted. Thus, Smith et al describes a method of introducing molecules into the interior of a selected cell type. Smith et al also discloses liposomes containing a molecule which is to be delivered. The liposome of Smith et al is targeted to a cell of choice by specific antibody interaction. The liposomes incorporate cytolytic peptides. In Smith et al, the liposome attaches to the target cell which then creates an endosome that takes the liposome into the cell, i.e., the liposome is now intracellular. The endosome is part of the mechanism by which the cell ingests food and is filled with acid as part of this process. The acid triggers the cytolytic peptide in the liposome to puncture the endosome and allow the liposome contents to enter the cell.

The foregoing amendment of claim 42 to incorporate the term "extracellular" clearly distinguishes the invention over Smith et al. Further, new claim 69 directed to detection of bacteria, is novel over Smith et al because bacteria do not form endosomes and, therefore, could not be the subject of the Smith et al technique.

In view of the above, reconsideration is requested.

Prior to addressing the specific rejections under 35 USC 103, Applicants offer the following.

As pointed out above, Smith et al does not relate to an analytical method of the type claimed in the claims as now presented. Additionally, the instant claims require that an extracellular metabolic signal be detected, i.e., the lipid vesicle particles remain outside the cell being detected. In contrast, the liposomes of Smith et al are "taken-up" by a cell to which a macromolecule is being delivered. As Applicants understand it, the liposomes of Smith et al do

not appear to respond to any kind of metabolic signal external to the target cell. In view of their incorporation into the targeted cell, the liposomes of Smith et al would not be capable of interacting with further reagents in the extracellular environment to provide an enhanced signal for detection. The "extracellular nature" of the present invention has a number of advantages in that the "species which is activated on said modulation of permeability" (see claim 42) is in an extracellular environment and can interact with further reagents in that environment, such as enzymes or fluorogenic or chromogenic reagents in that environment to provide an amplified signal indicating presence of the cell in the environment. As regards new claim 69, directed to bacteria, the subject matter of this claim could not have been obvious over Smith et al since bacteria do not form endosomes and could not have been the subject of the Smith et al technique.

Claim 50 stands rejected under 35 USC 103 as allegedly being obvious over Smith et al in light of Li et al. Withdrawal of the rejection is in order in view of the above-noted claim amendment and further in view of the comments that follow.

The distinctions between the present invention and Smith et al are detailed above. Li et al adds nothing that would have brought one skilled in the art closer to the instant invention. Accordingly, reconsideration is requested.

Claim 52 stands rejected under 35 USC 103 as allegedly being obvious over Smith et al. Withdrawal of the rejection is in order in view of the above-noted claim revisions and following comments.

Claim 52 depends from claim 42 and thus would have been unobvious for the reasons noted above. That is, Smith et al could not have suggested the presently claimed method since, in Smith et al, the liposomes are "taken-up" by a cell to which a macromolecule is being delivered.

Reconsideration is requested.

Claims 54-57 stand rejected under 35 USC 103 as allegedly being obvious over Smith et al in view of Levinson et al. Withdrawal of the rejection is order for the reasons that follow.

The failings of Smith et al are detailed above. Nothing in Levinson et al would have cured those failings. Reconsideration is requested.

Claims 58-59 and 61 stand rejected under 35 USC 103 as allegedly being obvious over Smith et al in view of Robinson et al. Withdrawal of the rejection is requested for the reasons that follow.

The deficiencies of Smith et al are discussed in detail above. Nothing in Robinson et al would have brought one closer to the instant invention. Reconsideration is requested.

Claims 58 and 60 stand rejected under 35 USC 103 as allegedly being obvious over Smith et al in view of Blondin et al. Withdrawal of the rejection is requested for the reasons that follow.

The fundamental distinctions between Smith et al and the instant invention are detailed above. Combining Smith et al and Blondin et al would not have rendered the claimed invention obvious. Reconsideration is requested.

Claims 65 and 66 stand rejected under 35 USC 103 as allegedly being obvious over Smith et al in view of Subbaro et al. Withdrawal of the rejection is requested for the reasons that follow.

The failings of Smith et al are detailed above. Nothing in Subbaro et al would have cured those failings. Reconsideration is requested.

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This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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